REMARKS

Claims 1 – 5, 7, 8, 14 and 45 - 47 are pending in the application. Claims 1, 7, 14, 45, and 46 have been amended. Claims 6, 9 – 13, 15 - 44 have been canceled as being directed to non-elected inventions. No new claims have been added. No new matter has been added by virtue of the amendments, support being found in the specification and in the claims as originally filed.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Interview

Applicants thank the examiner for the courtesy of the interview conducted on September 30, 2008 in which the claimed invention and the cited art was discussed. Agreement was not reached.

Claim Rejections- 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 45 and 47 under 35 USC §112, second paragraph as being indefinite. Applicants respectfully traverse the rejection.

The Examiner indicates "(t)he phrase 'wherein the inserting randomly comprises one or more of a method selected from: nuclease treatment, mechanical shearing, chemical treatment or radiation treatment in claim 45 is vague and renders the claim indefinite." (Office Action, p.2). The Examiner argues that "(i)t is unclear what is treated with one or more of a method selecting from: nuclease treatment, mechanical shearing, chemical treatment or radiation treatment (and) (i)t is unclear how those treatments correlate to inserting randomly." (Office Action, p.2). Applicants have amended the claims and respectfully disagree.

Claim 1 as amended recites a method for assembling a modulatable molecule, comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state, thereby generating a nucleic acid fusion molecule; and selecting a nucleic acid molecule that encodes a polypeptide wherein the state of the polypeptide encoded by the acceptor nucleic acid is coupled to the state of the polypeptide encoded by the insertion nucleic acid, or the state of the polypeptide encoded by the insertion nucleic acid is coupled to the state of the polypeptide encoded by the acceptor nucleic acid. Instant claims 45 depends from claim 1, and recites that the inserting randomly of **an insertion nucleic acid sequence into an acceptor nucleic acid sequence is carried out by** one or more of a method selected from: nuclease treatment, mechanical shearing, chemical treatment or radiation treatment.

Applicants submit that the amendments to the claims clarify that the methods selected from nuclease treatment, mechanical shearing, chemical treatment or radiation treatment refer to methods that are used in the random insertion of an insertion nucleic acid sequence into an acceptor nucleic acid sequence as set forth in the claims. Applicants direct the Examiner to the specification at paragraph [0130], where a number of different strategies can be used to create the fusion molecules of the instant invention, including nuclease treatment, mechanical shearing, chemical treatment or radiation treatment. Applicants refer the Examiner to paragraph [0140] of the application that teaches "it should be obvious to those of skill in the art that any method of introducing breaks into a DNA molecule can be used (e.g., such as digestion by mung bean nucleases, endonucleases, restriction enzymes, exposure to chemical agents, irradiation, and/or mechanical shearing)."

Claim Rejections- 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 45 and 47 under 35 USC §112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

The Examiner argues that "(c)laims 45 – 47 read on inserting randomly comprises one or more of a method selected from nuclease treatment, such as 3' to 5' exonuclease digestion, mechanical shearing, chemical treatment or radiation treatment (and) the phrase 'the inserting randomly comprises one or more of a method selected from nuclease treatment, mechanical shearing chemical treatment or radiation treatment is considered new subject matter." The Examiner contends that "(t)he claims encompass treating the insertion sequence or acceptor sequence or both with the recited treatment, however, the specification fails to provide sufficient support for treating the insertion sequence or acceptor sequence or both with the recited treatment." (Office Action, p.3-4).

Claim 1 and claim 45 have been set forth above. As amended, claim 1 features a method comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence. As amended, claim 45 recites that the random insertion is carried out by one or more of a method selected from: nuclease treatment, mechanical shearing, chemical treatment or radiation treatment.

Claim 45 recites and the specification supports the method as claimed. Applicants direct the Examiner to the specification, for example at paragraphs [0021], [0130], [0140], [0131], [0177] as previously pointed out. Applicants particularly point out paragraphs [0139] and [0140] below:

> **Construction of Random Insertion Libraries**
>
> In one aspect, a target vector comprising the nucleic acid encoding the acceptor polypeptide is randomly linearized (see, FIGS. 2B and 2C). A variety of different nucleases and digestion schemes can be used. For example, the vector may be exposed to DNase/Mn.sup.2+ digestion followed by polymerase/ligase repair; S1 nuclease digestion followed by polymerase/ligase repair; and S1 nuclease digestion which

> is not repaired. The three schemes differ in (a) the methods used to create the random double-stranded break in the target plasmid and (b) whether or not the nucleic acid (e.g., DNA) is repaired by polymerase/ligase treatment, or other methods. However, it should be obvious to those of skill in the art that any method of introducing breaks into a DNA molecule can be used (e.g., such as digestion by mung bean nucleases, endonucleases, restriction enzymes, exposure to chemical agents, irradiation, and/or mechanical shearing) and that the methods of introducing breaks described above are not intended to be limiting. [0139, emphasis added; 0140]

Applicants further point out paragraphs [0216] and [0217] which teach construction of Random Insertion Libraries using nuclease treatment.

> Construction of Random Insertion Libraries
>
> Plasmid pDIMC8-Mal was randomly linearized using three different methods: (1) DNase/Mn.sup.2+ digestion followed by polymerase/ligase repair; (2) S1 nuclease digestion followed by polymerase/ligase repair; and (3) S1 nuclease digestion (not repaired).

Accordingly, Applicants submit that the specification provides sufficient support for the invention as claimed. Applicants respectfully request that the rejection be withdrawn.

Claim Rejections- 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 45 - 47 under 35 USC §112, first paragraph, for allegedly failing to comply with the enablement requirement. The Examiner argues that "the specification, while being enabling for treating a nucleic acid with nuclease treatment, mechanical shearing, chemicals or radiation for the claimed method in vitro, does not reasonably provide enablement for treating a nucleic acid with nuclease, mechanical shearing, chemicals or radiation for the claimed method in vivo, or for treating any molecule other than nucleic acid. Applicants respectfully disagree.

As amended, the claims recite inserting randomly **an insertion nucleic acid sequence into an acceptor nucleic acid sequence** carried out by one or more of a method selected from nuclease treatment, mechanical shearing, chemical treatment or radiation treatment.

Applicants submit that the claims, as amended, are fully enabled, and respectfully request that the rejection be withdrawn.

Claim Rejections- 35 U.S.C. § 102 (b)

The Examiner has rejected claims 1 – 5, 7, 8 and 14 under 35 USC 102(b) as being anticipated by Lacatena et al. (PNAS, Vol. 91, pp.10521 – 10525. 1994). Applicants respectfully traverse the rejection.

As set forth above, the claims recite a method for assembling a modulatable molecule, comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state, thereby generating a nucleic acid fusion molecule; and selecting a nucleic acid molecule that encodes a polypeptide wherein the state of the polypeptide encoded by the acceptor nucleic acid is coupled to the state of the polypeptide encoded by the insertion nucleic acid, or the state of the polypeptide encoded by the insertion nucleic acid is coupled to the state of the polypeptide encoded by the acceptor nucleic acid.

To anticipate a claim, each and every element of the claim must be found in a single reference. This is discussed in the Manual of Patent Examining Procedure § 2131:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the . . . claim." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim,

but this is not an ipsissimis verbis test, i.e., identity of terminology is not required. In re Bond, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

The Lacatena reference does not teach or suggest all the limitations of the instant claims. In particular, the Lacatena reference does not teach or suggest **assembling a modulatable molecule**, comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, **wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state**, thereby generating a nucleic acid fusion molecule.

As pointed out by the Examiner, the Lacatena reference "teaches using TnphoA, a transposon probe for protein export signals, to generate hubeta2AR-phoA fusion protein in vivo by transposition of TnphoA into hubeta2AR gene in PUC18." (Office Action, p.9).

It is a feature of the instant invention, and it is recited in the claims, that the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state (e.g., such as an activity) (see at paragraph [0019]). Further, it is a feature of the instant invention, and it is recited in the claims, that the state of the polypeptide encoded by the acceptor nucleic acid is coupled to the state of the polypeptide encoded by the insertion nucleic acid, or the state of the polypeptide encoded by the insertion nucleic acid is coupled to the state of the polypeptide encoded by the acceptor nucleic acid.

The instant invention teaches that both the insertion sequence and acceptor sequence are capable of existing in at least two states and the state of the insertion sequence is coupled to the state of the acceptor sequence upon fusion, **such that a change in state in either the insertion sequence or acceptor sequence will result in a change in state of respective other portion of the fusion**. (see, e.g. paragraph [0073]). As taught by the specification at paragraph [0045], a "'state of a molecule' or a "state of a portion of a molecule" can be a conformation, binding affinity, or activity (e.g., including, but not limited to, ability to catalyze a substrate; ability to emit light, transfer electrons, transport or localize a molecule, modulating transcription, translation,

replication, supercoiling, and the like)." Further, as taught by the specification at paragraph [0048], "'coupled' refers to **a state which is dependent on another state such that a measurable change in the other state is observed**."

The Lacatena reference simply teaches a fusion molecule wherein the parts of the fusion- TnphoA and hubeta2AR do not each comprise a state, and where the state of TnphoA is coupled to the state of hubeta2AR, such that a measurable change in the other state is observed. Nowhere does the Lacatena reference teach **assembling a modulatable molecule**, comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, **wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state**, thereby generating a nucleic acid fusion molecule.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claim Rejections- 35 U.S.C. § 102 (e)

The Examiner has rejected claims 1 – 5, 7, 8 and 14 under 35 USC 102(e) as being anticipated by Anderson et al. (US Patent No. 6,596,485). Applicants respectfully traverse the rejection.

The claims were set forth above.

The Examiner argues that the Anderson reference "teaches generating random peptide by chemically synthesizing nucleic acid encoding the random peptide...(and) fusing random peptide into GFP to generate GFP fusion protein via insertion of nucleic acid." (Office Action, p.11).

The Anderson reference provides fusions of green fluorescent protein (GFP) and random peptides, and in particular, teaches a fusion nucleic acid comprising a first nucleic acid encoding a GFP scaffold protein; a second nucleic acid encoding a linker fused to the C-terminus of the scaffold protein and a third nucleic acid encoding a random peptide fused to the C-terminus of the linker. The GFP and the second and third nucleic acids taught by Anderson do not each comprise a state such that the state of one is coupled to the state of another such that a measurable change in the other state is observed.

Nowhere does the Anderson reference teach **assembling a modulatable molecule**, comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, **wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state**, thereby generating a nucleic acid fusion molecule.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claim Rejections- 35 U.S.C. § 102 (b)

The Examiner has rejected claims 1 – 5, 7, 8 and 14 under 35 USC 102(b) as being anticipated by Manoil et al. (J of Bacteriology vol. 172, No. 2 p.515 - 518). Applicants respectfully traverse the rejection.

The claims were set forth above.

Nowhere does the Manoil reference teach **assembling a modulatable molecule**, comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, **wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state**, thereby generating a nucleic acid fusion molecule.

Accordingly, Applicants respectfully request that the rejection be withdrawn

The Examiner has rejected claims 1 – 5, 7, 8 and 14 under 35 USC 102(b) as being anticipated by Mountford et al. (TIG, Vol 11, No.5, p. 179 - 184). Applicants respectfully traverse the rejection.

The claims were set forth above.

Nowhere does the Mountford reference teach **assembling a modulatable molecule**, comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, **wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state**, thereby generating a nucleic acid fusion molecule.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claim Rejections- 35 U.S.C. § 102 (e)

The Examiner has rejected claims 1 – 5, 7, 8 and 14 under 35 USC 102(e) as being anticipated by Ong et al. (US Patent No. 6,687,035). Applicants respectfully traverse the rejection.

The claims were set forth above.

Nowhere does the Ong reference teach **assembling a modulatable molecule**, comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, **wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state**, thereby generating a nucleic acid fusion molecule.

Accordingly, Applicants respectfully request that the rejection be withdrawn

The Examiner has rejected claims 1 – 5, 7, 8 and 14 under 35 USC 102(e) as being anticipated by Heintz et al. (US Patent No. 6,485,912). Applicants respectfully traverse the rejection.

The claims were set forth above.

Nowhere does the Heintz reference teach **assembling a modulatable molecule**, comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, **wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state**, thereby generating a nucleic acid fusion molecule.

Accordingly, Applicants respectfully request that the rejection be withdrawn

Claim Rejections- 35 U.S.C. § 103(a)

Claims 1 and 45 - 47 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Anderson et al. (as above), in view of Norris, 2006 (US Patent No. 7,135,176). Applicants respectfully traverse the rejection.

Claim 1 was set forth above.

The Anderson et al. reference fails to teach or suggest all the elements of the instant invention. In particular, nowhere does the Anderson reference teach **assembling a modulatable molecule**, comprising inserting randomly an insertion

nucleic acid sequence into an acceptor nucleic acid sequence, **wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state**, thereby generating a nucleic acid fusion molecule.

The Norris reference does not cure the defect of the Anderson reference. Nowhere in the Norris reference is there teaching or suggestion of **assembling a modulatable molecule**, comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, **wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state**, thereby generating a nucleic acid fusion molecule. Therefore, the teachings of the cited art, when combined, do not result in the claimed invention.

Accordingly, Applicants request that the rejection be withdrawn.

CONCLUSIONS

For the reasons provided, Applicant submits that all claims are allowable as written and respectfully requests early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

The Director is hereby authorized to charge any credits or deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to Deposit Account No. 04-1105.

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